Urological Science xxx (2016) 1–4

Contents lists available at ScienceDirect

Urological Science

journal homepage: www.urol-sci.com

Original article

Single session of high-intensity focused ultrasound therapy for the management of organ-confined prostate cancer: A single-institute experience

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ARTICLE INFO

Article history:
Received 20 April 2016
Received in revised form
4 July 2016
Accepted 3 September 2016
Available online xxx

Keywords:
high-intensity focused ultrasound
localized
nadir
prostate cancer
prostate-specific antigen

ABSTRACT

Objective: The aim of this study was to evaluate the therapeutic response and complications of high-intensity focused ultrasound for patients with localized prostate cancer.
Materials and Methods: We evaluated the clinical outcomes of 29 patients who received high-intensity focused ultrasound as first-line treatment for localized prostate cancer at our hospital from October 2010 to March 2016. Biochemical recurrence was defined, according to the Stuttgart definition of biochemical failure, as the prostate-specific antigen nadir plus 1.2 ng/mL. Prostate-specific antigen levels and complications were recorded during regular follow-up.
Results: The mean follow-up period was 24.6 months. Six patients experienced biochemical recurrence (20.68%). Disease progression was noted in six patients (20.68%), and salvage therapy was performed in these patients. The 24.6-month cancer-specific survival rate was 100%. No severe complications were reported.
Conclusion: High-intensity focused ultrasound is an alternative therapy for patients with localized prostate cancer. In combination with preceding transurethral resection of the prostate, this treatment shows promise in disease control with a low complication rate in short-term follow-up.

1. Introduction

Prostate cancer was among the most frequently diagnosed tumors among men in the United States in 2014.[1] For patients with localized disease, radical surgery including radical prostatectomy, laparoscopic prostatectomy, or robotic-assisted radical prostatectomy should be considered. Brachytherapy and external beam radiation therapy are regarded as equally effective against localized disease.[2] However, these therapeutic approaches can result in complications that can affect the quality of life.[3] Patients with multiple comorbidities are at high risk when undergoing radical surgery. Consequently, the need for minimally invasive treatments for localized prostate cancer, such as high-intensity focused ultrasound (HIFU) and cryotherapy, has increased in recent years.

Hyperthermia and cavitation are the two major mechanisms by which HIFU can be used to treat localized prostate cancer.[4] The therapeutic effect of HIFU on human prostate cancer *in vivo* was first described in 1995.[5] Study results showed that HIFU was an effective, minimally invasive treatment for prostate cancer. Over time, as technology improved, HIFU became a more accessible therapeutic option for patients with localized prostate cancer. Nonetheless, HIFU is not routinely recommended owing to a lack of prospective, randomized, and controlled clinical trials with sufficient follow-up in the medical literature.[6,7]

Here, we present a single-center experience of 29 patients with localized prostate cancer treated with HIFU between October 2010 and March 2016. Oncological outcomes and complications are also discussed in relation to the literature.

2. Materials and methods

This study involved 29 patients with localized prostate cancer who received HIFU as first-line therapy at Tri-Service General

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http://dx.doi.org/10.1016/j.urols.2016.09.002

Hospital, Taipei, Taiwan, between October 2010 and March 2016. General characteristics, prostate-specific antigen (PSA) levels, and clinical staging data were collected prospectively from patient medical records. We established the following inclusion criteria: localized prostate cancer, clinical stages T1N0M0–T2N0M0, no previous hormone therapy (HT) or radiation therapy, and lack of suitability for radical prostatectomy due to multiple comorbidities or high risk for surgical complications. Our exclusion criteria included locally advanced disease, metastatic disease, and rectal wall disease. The diagnosis of prostate cancer was established by transrectal ultrasound (TRUS)-guided needle biopsy of the prostate. Clinical staging was determined on the basis of magnetic resonance imaging of the pelvis and a whole-body bone scan. According to the results of clinical stage, Gleason score, and PSA levels, patients were classified into risk groups according to the National Comprehensive Cancer Network recurrence risk stratification guidelines. Patients first underwent transurethral resection of the prostate (TURP), and then returned 4 weeks later to receive HIFU therapy.

The Ablatherm HIFU device (EDAP TMS, Vaulx-en-Velin, France) is composed of a treatment module, a control module, and a probe with both image and treatment transducers. After the administration of general or spinal anesthesia, the patient is transferred to the treatment module and placed in the right lateral decubitus position. The probe is then introduced into the rectum for a pretreatment evaluation using an ultrasound image. The prostate cancer will be observed as a hypoechoic lesion under the image transducer before treatment. Depending on the tumor location and volume, a personalized therapeutic strategy is designed by adjusting the parameters of the control module. Using the HIFU system, the treatment process may be performed automatically. During HIFU therapy, a hypoechoic lesion will change to a hyperechoic lesion in which we can evaluate the degree of destruction in real time.[8]

Following whole-gland ablation with HIFU, suprapubic cystostomy was performed in the study patients. Two days later, the Foley catheter was removed, and patients were discharged. Follow-up was arranged by our outpatient department. The suprapubic cystostomy tube was removed 1 week after discharge during the first outpatient department visit. Patients were subsequently seen every month, and their PSA levels were checked every other month. The PSA nadir was defined as the lowest level during follow-up. Oncological outcomes were assessed on the basis of biochemical failure and cancer-specific survival rate. The Stuttgart definition of biochemical failure was used to define biochemical recurrence (PSA nadir plus 1.2 ng/mL).[9] Repeated TRUS-guided needle biopsy was recommended if biochemical failure developed. Salvage therapy would be arranged in the event of biochemical recurrence even if the result of TRUS-guided needle biopsy of the prostate was negative. HIFU-related complications were also recorded during outpatient department follow-up.

3. Results

3.1. Patients

This study included 29 patients diagnosed with localized prostate cancer who received HIFU therapy at Tri-Service General Hospital between October 2010 and March 2016. Characteristics of the 29 patients with localized prostate are shown in Table 1. The mean age was 68.1 years, and the mean follow-up duration was 24.6 months. The mean PSA level was 10.3 ng/mL. The predominant clinical stages were T1cN0M0 (19 patients, 65.5%) and T2cN0M0 (4 patients, 13.79%). Almost all patients underwent TURP (27 patients, 93.1%) before HIFU therapy. According to National Comprehensive Cancer Network guidelines, the majority of patients were classified to be at intermediate risk (14 patients, 48.27%). However, four patients were lost to follow-up due to relocation.

Table 1
Characteristics of 29 patients with localized prostate.

Age (y)	68.1 (59–82)
PSA (ng/mL)	10.3 (0.5–31.5)
Clinical stage	
cT1a	1 (3.44)
cT1b	3 (10.34)
cT1c	19 (65.5)
cT2a	1 (3.44)
cT2b	1 (3.44)
cT2c	4 (13.79)
TURP before HIFU	
No	2 (6.89)
Yes	27 (93.1)
Gleason score	
≤6	16 (55.17)
7	12 (41.37)
>7	1 (3.44)
NCCN risk groups	
Low risk	11 (37.93)
Intermediate risk	14 (48.27)
High risk	4 (13.79)
Median prostate volume (mL)	27.15 (9.32–59.6)

Data are presented as *n* (%) or mean (range), unless otherwise indicated.
HIFU = high-intensity focused ultrasound; NCCN = national comprehensive cancer network; PSA = prostate-specific antigen; TURP = transurethral resection of the prostate.

3.2. Treatment

Patients were treated with the Ablatherm HIFU device (EDAP TMS) between October 2010 and March 2016. Most patients underwent a single HIFU session, although three patients (10.34%) underwent a second HIFU session due to biochemical failure or biopsy-proven malignancy.

3.3. Oncological outcomes

Postoperative outcomes and complications are shown in Table 2. The mean PSA nadir was 0.21 ng/mL and was achieved within a mean of 1.9 months after HIFU therapy. Undetectable PSA levels were noted in 16 patients. Only three patients had PSA nadir levels greater than 1 ng/mL. One of these patients displayed biochemical recurrence 6 months later and underwent TRUS-guided needle biopsy that revealed adenocarcinoma of the prostate. Secondary HIFU was arranged immediately for disease control, but owing to progression of the PSA level, salvage radiation therapy was performed. The second patient with a PSA nadir of > 1 ng/mL underwent HT for bone metastasis. The third patient experienced

Table 2
Postoperative outcomes and complications.

Mean time to PSA nadir (d)	57.96
PSA nadir (ng/mL)	0.2116
Undetectable (<0.04 ng/mL)	16
Detectable (ng/mL)	13
<1	10
>1	3
Secondary biopsy	5
Complications	
Urinary tract infection	6 (20.6)
Urethral stricture	8 (27.58)
Erectile dysfunction	7 (24.13)
Bladder neck contracture	7(24.13)

Data are presented as *n* or *n* (%).
PSA = prostate-specific antigen.

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biochemical recurrence 1 year later and received secondary HIFU. The cancer-specific survival rate was 100% and the metastasis-free survival rate was 96.55%.

3.4. Safety

During the operation, no immediate complications developed in any patients. Postoperative complications included urinary tract infection, urethral stricture, erectile dysfunction, and bladder neck contracture. The most common complication was urethral stricture. Prostatitis was observed in only one patient who did not undergo preceding TURP.

4. Discussion

Although HIFU has been used to treat prostate cancer for more than 20 years,[5] the role of HIFU in the treatment of localized prostate cancer is still controversial. According to the European Association of Urology and American Urological Association guidelines, HIFU has therapeutic effects in localized prostate cancer. However, this therapy has not been routinely recommended, owing to the lack of prospective and randomized controlled trials with long-term follow-up conducted until recently.[6,7]

Table 3 shows the findings of our study and the recent studies related to the results of long-term follow-up after HIFU treatment for prostate cancer. Adenocarcinoma of the prostate was proved by TRUS-guided needle biopsy. No nodal or distant metastasis was found on image evaluation. The initial mean PSA level was < 15 ng/mL. Neoadjuvant HT was used in 29–44% of men, and preceding TURP was used in 20–93% of men. The PSA nadir (0.03–0.55 ng/mL) was achieved within 5 months after primary HIFU therapy. The biochemical recurrence rate was defined using various criteria. These studies also showed excellent cancer-specific survival rates of 90–100% on long-term follow-up. In our study, similar oncological outcomes including low biochemical recurrence (20.68%) and high cancer-specific survival rates (100%) were also noted. However, the short follow-up period and the small number of cases are the major limitations of the current study.

Owing to the limited evidence regarding neoadjuvant HT before HIFU for localized prostate cancer,[6,7] we did not perform this therapy before HIFU in all patients. Komura et al[10] demonstrated that neoadjuvant HT followed by HIFU renders cancer manageable by reducing the prostate volume and resulting in more rapid achievement of the PSA nadir. By contrast, the use of neoadjuvant HT did not result in any significant difference in the 5-year biochemical recurrence-free survival rate in a study by Ganzer et al.[11] However, currently, the use of neoadjuvant HT before HIFU for localized prostate cancer seems safe and feasible.

HIFU therapy is not suitable for large-volume localized prostate cancer because of the short therapeutic length of about 19–26 mm.[8] In order to increase the application of HIFU therapy in prostate cancer, preceding TURP has been performed since 2000,[12] and Rebillard et al[13] showed the beneficial effect of this therapy in shrinking prostate volume, removing calcification, decreasing the catheterization period, and reducing complications. In our series, only two patients did not receive preceding TURP owing to a relatively small prostate volume. All patients experienced bladder outlet obstruction and underwent surgical intervention. Routine preceding TURP may be considered not only for the prevention of complications, but also for whole-gland therapy.

The PSA nadir has been described as a predictive factor for oncological failure of localized prostate cancer after HIFU therapy.[12,14] In our study, a PSA nadir of > 1 ng/mL was found in three patients. Two of these patients were at high risk, and the other patient was at intermediate risk. They all received salvage treatment and experienced promising disease control. Thüroff and Chaussy[12] demonstrated that the PSA nadir is the greatest predictor of biochemical failure. In their study, the PSA nadir was obtained at a mean of 2.1 months after treatment, which is standard following tumor ablation. If the nadir is < 0.3 ng/mL, the 5-year biochemical disease-free survival rate is 94%. Crouzet et al[15] showed similar results in that the 5-year biochemical disease-free survival rate was 91% in patients with a PSA nadir of < 0.3 ng/mL. Their study also showed that the cut-off value for PSA levels after HIFU therapy for early control biopsy was 0.3 ng/mL in most hospitals. However, the cutoff value of PSA nadirs for predicting treatment failure remains controversial.[16]

Salvage treatment after HIFU therapy should be considered in patients with local recurrence or biochemical failure according to the results of prostate biopsy, bone scan, and magnetic resonance imaging.[17] Ganzer et al[11] performed HIFU therapy in 538 patients with localized prostate cancer. Ninety-seven patients (18%) received salvage therapy including HT, radiation therapy, chemotherapy, and radical prostatectomy. Significantly fewer patients at low risk underwent salvage therapy. We also used salvage therapy for patients with disease progression. Table 4 shows the effects of salvage therapy for disease recurrence in our series. Secondary HIFU for local recurrence and HT for bone metastasis showed promising results for disease control. However, three patients experienced PSA progression without positive findings of magnetic resonance imaging, bone scan, and prostate biopsy. Management of biochemical failure in prostate cancer is controversial, and about one-third of these patients will develop distal metastasis eventually.[18] Androgen deprivation therapy was prescribed, and acceptable disease control with decreasing PSA levels was found.

Table 5 shows the complications after HIFU therapy for localized prostate cancer in our study and in recent studies. Complications including urinary retention, bladder neck stenosis, urethral stricture, chronic pelvic discomfort, and epididymitis have been described.[8] Along with the improvements in the HIFU device and the utility of preceding TURP, a decreasing incidence of complications has also been noted.[13] For example, rectal fistulas are rarely found after integrating the use of imaging with HIFU devices.[12] In

Table 3
Case series of HIFU for localized prostate cancer and outcome.

MFSR (%)	96.55 (25 mo)	99.4 (5 y)	70 (10 y)	>95 (10 y)	95 (10 y)	94 (10 y)
CSSR (%)	100 (25 mo)	100 (5 y)	90 (10 y)	>95 (10 y)	99 (10 y)	97 (10 y)
Biochemical failure (%)	20.68 (Stuttgart)	25.7 (Stuttgart)	46 (Stuttgart)	<39 (Phoenix)	N/A	21.1 (Phoenix)
Nadir/time to nadir	0.21/1.9 mo	0.03/2.5 mo	0.55/4 mo	0.4/20 wk	0.1/2.1 mo	0.14/7.9 wk
PSA	10.3 (mean)	7.7 (median)	12.1 (mean)	11.2 (mean)	9.9 (mean)	7.7 (median)
Follow-up (mo)	24.6 (mean)	43 (median)	94 (median)	97 (mean)	63 (mean)	78 (median)
Clinical stage	T1N0M0–T2N0M0	T1N0M0–T2N0M0	T1N0M0–T2N0M0	T1N0M0–T3N0M0	T1N0M0–T2N0M0	T1N0M0–T3N0M0
Mean age (y)	68.1	68.3	76.1	67.7	68.4	71
Patient No.	29	171	110	538	704	1002
Case series	Our series	Komura et al[10]	Limani et al[14]	Ganzer et al[11]	Thüroff & Chaussy[12]	Crouzet et al[14]

CSSR = cancer-specific survival rate; HIFU = high-intensity focused ultrasound; MFSR = metastasis free survival rate; PSA = prostate-specific antigen.

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Table 4
Salvage therapy for disease recurrence after HIFU treatment in our series.

Patient No.	PSA Gleason score Clinical stage	PSA nadir/max. PSA following HIFU	Evaluation	Treatment	Latest PSA
1	26.9 3 + 4 T1cN0M0	1.09/2.59	MRI (−) Bone scan (−) Biopsy (+)	HIFU RT	<0.04
2	11.4 5 + 5 T2cN0M0	1.57/2.21	MRI (+) Bone scan (+) Biopsy (−)	HT	<0.04
3	10.63 3 + 4 T1cN0M0	1.14/2.34	MRI (−) Bone scan (−) Biopsy (−)	HIFU	0.1
4	15 3 + 4 T2cN0M0	<0.04/1.85	MRI (+) Bone scan (−) Biopsy (−)	HIFU	0.85
5	3.9 3 + 4 T1cN0M0	0.1/1.34	MRI (−) Bone scan (−) Biopsy (−)	HT	0.24
6	7.7 3 + 4 T1cN0M0	0.73/1.91	MRI (−) Bone scan (−)	HT	1.34

HIFU = high-intensity focused ultrasound; HT = hormone therapy; MRI = magnetic resonance imaging; PSA = prostate-specific antigen; RT = radiation therapy.

Table 5
Case series of HIFU for localized prostate cancer considering the complications.

Case series	BOO (%)	SUI (%)	Impotency (%)	Fistula (%)	UTI (%)
Our series	48.27	17.24	24.13	0	20.6
Blana et al[9]	11.7	5.8	52.7	0.7	4.8
Limani et al[14]	21	11	30.8	0.9	18
Ganzer et al[11]	28.3	20.1	35	0.7	10.2
Thüroff & Chaussy[12]	21.4	3.26	45	0.28	2.1
Crouzet et al[14]	16.6	23.7	57.7	0.4	3.9

BOO = bladder outlet obstruction; HIFU = high-intensity focused ultrasound; SUI = stress urinary incontinence; UTI = urinary tract infection.

our study, no rectal fistulas were observed in the 29 patients. To avoid acute urinary retention and decrease the catheterization period, suprapubic cystostomy was performed in all patients before HIFU therapy.

This study focused on the results of HIFU treatment of localized prostate cancer. A low biochemical recurrence rate (20.68%), acceptable complication rates, and a high cancer-specific survival rate (100%) were obtained. However, the short follow-up period of 24.6 months and the small number of cases are limitations of this study. Therefore, long-term benefits of HIFU for localized prostate cancer should be evaluated in further well-designed randomized controlled trials.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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